Public Health Goal for HEXACHLOROCYCLOPENTADIENE In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR HEXACHLORO-CYCLOPENTADIENE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.05 mg/L (50 ppb) for hexachlorocyclopentadiene, also known as HEX, in drinking water. The California Maximum Contaminant Level (MCL) is 0.05 mg/L (50 ppb) for HEX in drinking water. The PHG is based on noncancer toxic effects in a 13-week oral study. Hexachlorocyclopentadiene was administered in corn oil by gavage to groups of 10 male and 10 female rats and mice once daily, five days per week for 13 weeks. Deaths due to HEX intoxication occurred at 150 and 300 mg/kg in mice and stomach lesions of hyperplasia and focal inflammation were observed in male and female mice and male rats at and above 19 mg/kg (Abdo *et al.*, 1984; U.S. EPA, 1992). From this study, a NOAEL of 10 mg/kg-day was identified. A factor of 1,000 (10-fold for inter-species variation, 10-fold for human variability, and 10-fold to account for the use of a subchronic study for determining a lifetime value and dose by gavage) was used to account for uncertainty and differences from daily exposure.

INTRODUCTION

The purpose of this document is to develop a PHG for hexachlorocyclopentadiene. Hexachlorocyclopentadiene, sometimes abbreviated as “HEX,” is an unsaturated, highly reactive, chlorinated hydrocarbon of low water solubility. HEX is used in the manufacture of chemicals and products and has no end uses of its own (U.S. EPA, 1992).

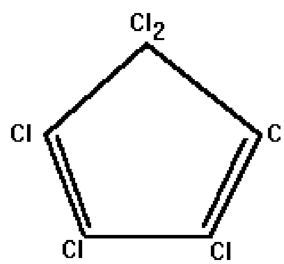
Hexachlorocyclopentadiene is easily degraded and not frequently found in the environment. The degradation products have not been identified (U.S. EPA, 1992). Generally, human exposure to HEX via air, soil, or water is expected to be minimal with the exception of persons living or working near areas in which HEX is manufactured, transported or handled. Occupational exposure is the most likely source of human exposure (WHO, 1991a).

CHEMICAL PROFILE

Chemical Identity

Hexachlorocyclopentadiene is an oily, lemon-yellow to yellow-green organic liquid that has a pungent, musty odor. It easily volatilizes from a liquid to a vapor when exposed to air (ATSDR, 1997; U.S. EPA, 1995). Hexachlorocyclopentadiene is a five-carbon ring with six chlorine atoms attached as shown in Table 1. The chemical formula, synonyms and identification numbers are listed in Table 1.

Table 1. **Chemical Identity of Hexachlorocyclopentadiene**

Hexachlorocyclopentadiene	**Identification Attribute**
Chemical Name	hexachlorocyclopentadiene
Synonyms	HEX, HCCPD, perchlorocyclopentadiene
Registered trade name	C-56, HRS 1655
CAS registry number	77-47-4
Chemical formula	C_5Cl_6
Wiswesser line notation	L5 AHJ AG AG BG CG DG EG
Chemical structure	

Physical and Chemical Properties

We list physical and chemical properties of hexachlorocyclopentadiene in Table 2. Hexachlorocyclopentadiene is only slightly soluble in water and is poorly volatile.

Table 2. **Physical and Chemical Properties of Hexachlorocyclopentadiene**

Property	**Value or Information**	**Reference**
Molecular weight	272.75	(ACGIH, 1992)
Color	Yellow/green	(U.S. EPA, 1995)
Physical state	Liquid	(U.S. EPA, 1995)
Odor	Pungent	(U.S. EPA, 1995)
Odor threshold	0.0014-0.0016 mg/m^3	(WHO, 1991a)
Melting point	-9 ^oC	(ACGIH, 1992)
Boiling point	238 ^oC	(ACGIH, 1992)

Property	Value or Information	Reference
Flammability limits	Noncombustible	(NIOSH, 1994)
Autoignition temperature	Noncombustible	(NIOSH, 1994)
Solubility		
Water	2 mg/L @ 25 ^oC, insoluble	(U.S. EPA, 1995)
Organic solvents	Soluble in acetone, carbon tetrachloride and hexane	(U.S. EPA, 1995)
Specific Gravity	1.7 @ 25 ^oC	(U.S. EPA, 1995)
Partition coefficient		
reported range Log K_{ow}	log K_{OW} = 3.99 - 5.04	(U.S. EPA, 1984; U.S. EPA, 1995)
Vapor pressure	0.08 torr @ 25 ^oC	(ACGIH, 1992)
Henry's law constant	$2.7x10^{-2}$ atm-m^3/mole	(U.S. EPA, 1995)
Conversion factors	1 ppm =3.83 mg/m^3	(NIOSH, 1994)

Production and Uses

Hexachlorocyclopentadiene is made from chlorination of cyclopentadiene or by removing chlorine from octachlorocyclopentane. HEX is an intermediate in the manufacture of certain chlorinated pesticides, flame retardant textiles, shock-proof plastics, esters, ketones, fluorocarbons, and dyes (ATSDR, 1997; WHO, 1991a). Commercially available HEX contains several impurities including octachlorocyclopentene, hexachlorobenzene, and lower chlorinated cyclopentadienes (WHO, 1991a).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Hexachlorocyclopentadiene does not occur naturally in the environment (WHO, 1991b).

Few data are available on relative contribution of various sources to the environment. Human exposure is not significant, except for those living or working near manufacturing, shipping, or disposal of HEX. Occupational exposure is the most likely source of human exposure (WHO, 1991b).

Air

Hexachlorocyclopentadiene is rapidly degraded in the atmosphere and is generally thought to be undetectable in ambient outdoor air (ATSDR, 1997). Those residing or working near hazardous waste disposal areas in which hexachlorocyclopentadiene or HEX-derived chemicals were disposed might be exposed to airborne HEX. ATSDR (1997) cites one source as measuring HEX levels ranging from 0.032 to 0.053 ppb in the air near a hazardous waste disposal site. HEX has also been found in the air near treatment facilities with HEX use or manufacturing industrial sources upstream, most notably when large amounts of the compound were dumped into the water upstream from the treatment facility (ATSDR, 1997; U.S. EPA, 1992).

In 1977, ninety-seven municipal sewage plant workers became ill from airborne exposure to hexachlorocyclopentadiene following HEX contamination upstream from the sewage plant (Kominsky *et al.*, 1980; Morse *et al.*, 1979). This was an industrial exposure to airborne HEX which volatilized from contaminated water; and it involved some toxic chemicals other than HEX.

Airborne hexachlorocyclopentadiene is expected to react rapidly with hydroxyl and nitrate radicals and with ozone. HEX is also expected to be degraded by photolysis. The half-life of HEX in air is estimated at less than 1 day (ATSDR, 1997; Grosjean and Williams, 1992).

Soil

Ambient monitoring data for HEX in soil are not available, however the U.S. Environmental Protection Agency (U.S. EPA) predicts these levels should be lower than those concentrations present in the aquatic environment since deposition of HEX from the air or water into the terrestrial medium is expected to be minimal (U.S. EPA, 1984).

Degradation of HEX occurs in both sterile and nonsterile soil systems with nonsterile aerobic and anaerobic conditions apparently producing a faster degradation rate, indicating that biodegradation of HEX occurs in soil (U.S. EPA, 1984; ATSDR, 1997). HEX in soil is presumed to be tightly adsorbed to organic mater and relatively resistant to leaching into water within the soil. The primary routes of transport are movement of particles on to which HEX is bound and volatilization into the atmosphere (U.S. EPA, 1984).

Water

HEX is poorly soluble in water and volatilizes from the water surface, especially turbulent water (WHO, 1991a). HEX in water degrades rapidly due to photolysis, hydrolysis, and biodegradation (WHO, 1991b). In deeper, non-flowing bodies of water, hydrolysis and biodegradation may become the predominant removal mechanisms for waterborne HEX (WHO, 1991b).

Releases of HEX to water can occur during manufacture, use, or disposal of the chemical (ATSDR, 1997). The atmospheric residence time of hexachlorocyclopentadiene is probably short, and the Henry’s law constant predicts higher concentrations in the vapor phase. Accordingly, transport of HEX to water systems via deposition from the atmosphere or by soil runoff is not considered likely or significant (U.S. EPA, 1980).

HEX is usually not detectable in water samples except when taken in specific bodies of water near known points of industrial discharge (U.S. EPA, 1980). No reliable data exist on HEX levels in drinking water or untreated impounded water (U.S. EPA, 1984; U.S. EPA, 1984). Concentrations of HEX in wastewater from a production plant ranged from 156-18,000 ppb. (ATSDR, 1997; U.S. EPA, 1980). In shallow water HEX has a photolytic half-life of less than one hour (U.S. EPA, 1992).

Food

No data were located regarding sampling and analysis of hexachlorocyclopentadiene levels in human food sources. Exposure of the general population to HEX via any environmental medium is extremely low (ATSDR, 1997; U.S. EPA, 1992), and information regarding general human exposure to HEX via food is not available (U.S. EPA, 1984).

Other Sources

Bioaccumulation, which can be thought of as the net result of the absorption rate and the elimination rate of a compound (U.S. EPA, 1984), is an important determinant of the level and duration of human exposure. The log octanol/water partition coefficient was experimentally determined as ranging between 3.99 and 5.04 which suggests a potential for bioconcentration, bioaccumulation, and biomagnification, meaning that the chemical has a theoretical potential to accumulate and concentrate in living organisms (U.S. EPA, 1984; U.S. EPA, 1995; Wolfe *et al.*, 1982). Actual investigations into biological accumulation of hexachlorocyclopentadiene revealed that HEX does not accumulate significantly as it is readily metabolized (U.S. EPA, 1984; Podowski *et al.*, 1991). In 1975, Lu *et al.* investigated environmental stability of HEX in an aquarium model ecosystem concluding that the volatility of the chemical accounted for the relatively low amounts in the various organisms (Lu *et al.*, 1975). More current thinking agrees that bioconcentration of HEX may occur to a small extent, but biomagnification through the food chain is not likely because HEX degrades readily via photolysis and hydrolysis reactions as well as biodegradation in the water, soil, and sediment media, in addition to volatilization from surfaces (ATSDR, 1997).

METABOLISM AND PHARMACOKINETICS

Absorption of HEX in animals occurs through the lungs, the gastrointestinal tract and skin, with gastrointestinal absorption relatively poor due to the binding of HEX to the gastrointestinal contents. Once absorbed, HEX is distributed to the liver, kidneys, and lungs; and tends to accumulate in the adipose tissue (ATSDR, 1997). No data are available on absorption of HEX by humans by any route of exposure.

Absorption

According to ATSDR (1997), the route of exposure has a significant effect on the absorption of HEX in the rat, with relatively low amounts of HEX appearing in the blood following oral dosing compared with higher levels via the intravenous and inhalation routes. Presumably, this is why HEX is about 100 times more toxic when inhaled compared with the ingestion route and its associated reactions with gastrointestinal membranes, tissues and contents (U.S. EPA, 1992). Differential absorption of HEX via the various routes of administration is key to the differential toxicity and is discussed here in some detail.

Several investigators have examined the differences between orally administered and inhaled HEX in laboratory animals (Lawrence and Dorough, 1981; Lawrence and Dorough, 1982; Dorough and Ranieri, 1984). Lawrence and Dorough (1982) studied the effects of different routes of exposure on absorption, distribution, and ultimate fate of HEX in laboratory rats.

The researchers found that 72 hours after a single oral dose of HEX, 68.2 percent of the radiocarbon from orally administered HEX was excreted via the fecal route. In the same study, only 31.4 percent of the radiocarbon from inhaled HEX and 23.1 percent of the carbon from intravenously administered HEX were fecally eliminated, indicating relatively poor absorption via the oral route.

El Dareer *et al*. (1983) confirmed Lawrence and Dorough's results in the rat, and also concluded that the reaction of HEX with intestinal contents and its apparent lack of absorption in intact form most probably accounts for the relatively low toxicity of oral doses.

The differences in absorption of hexachlorocyclopentadiene, via the inhalation versus the oral route of administration, impact the distribution and elimination of hexachlorocyclopentadiene.

Distribution

As mentioned above, the route of exposure of hexachlorocyclopentadiene in animals influences absorption and thus influences distribution and toxic response. OEHHA focuses attention principally on the oral route, although we describe other routes for comparison.

In 1984, Dorough and Ranieri examined the distribution and elimination of HEX in rats and mice following a single oral dose and also as a component of the diet for a maximum of 30 days. When fed HEX continuously, rats and mice accumulated ^{14}C radiocarbon in the kidney, liver, ovaries and fat fairly uniformly between sexes, although female animals have a tendency for somewhat higher tissue HEX levels than do males. In rats, the kidney contained the highest residues whereas the liver contained the highest residues in mice. The material was found sparingly or not-at-all in muscle, brain, and gonads. Once exposure ceased in the diet-treated group, tissue levels decreased quickly for all tissues except fat.

El Dareer *et al*. (1983) compared and contrasted the basis for differential toxicity from HEX administration to rats via the oral, inhalation, and intravenous routes of exposure. Distribution of radioactivity was measured 72 hours following HEX administration. For the orally dosed group, greater than 90 percent of the radioactivity appeared in urine and feces, with feces containing 2.2 times as much radioactivity as urine. Only about 2.4 percent of the radiolabel was found within the tissues of the orally dosed rats. For intravenous exposures, 39 percent of the radiolabel appeared within the tissues (El Dareer *et al.*, 1983).

Seventy-two hours following inhalation exposure, 11.5 percent of the radiolabel was found within the tissues; this level was down from the nearly 30 percent measured 6 hours following exposure. For comparison of distribution, 72 hours following oral administration of HEX, only small amounts (2.4 percent) remained within the tissues. Most of this remaining material was found in the liver (0.6 percent) and the kidney (0.7 percent).

Seventy-two hours following intravenous administration, most of the radiolabel was found in the liver and the carcass (animal body minus organs). At 72 hours after dosing with ^{14}C HEX vapors, percentages of radiolabel remaining (which were greater than those from oral dosing and less than those from i.v. administration) were highest in the blood, the kidneys, the lungs and the carcass.

Metabolism and Excretion

Limited studies on the pharmacokinetics of hexachlorocyclopentadiene appear in the literature. The studies examine the disposition and fate of ^{14}C-labeled HEX and describe total radioactivity, rather than metabolic products of HEX. No metabolites of HEX have been unequivocally identified, however some characteristics such as polarity and solubility have been described (U.S. EPA, 1992; ATSDR, 1997). Data on metabolism of HEX are quite limited (ATSDR, 1997). Generally, orally administered HEX is metabolized by bacteria in the gut (Yu and Atallah, 1981; Dorough and Ranieri, 1984). Metabolites in urine and feces are difficult to identify due to presence of co-extracted compounds of a polar nature (Yu and Atallah, 1981). The extraction characteristics of the radiolabel in the excreta showed that the metabolites were mostly polar, some of which could be changed to organic soluble compounds by acid catalyzed hydrolysis (Dorough and Ranieri, 1984).

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

Acute oral toxicology. In 1955, Treon *et al*. determined acute oral LD_{50} in two species, female rabbits and rats of both sexes. Hexachlorocyclopentadiene was administered as a five percent solution in peanut oil by oral gavage. The oral LD_{50} for male Carworth rats was determined to be 505 mg/kg. The oral administration of HEX induced diarrhea, lethargy, and a retarded respiratory rate. At sufficient dosage levels, intoxication resulted in death after one to two days. Rabbits and rats given lethal oral dosages of HEX exhibited diffuse degenerative lesions of the brain, heart, liver and adrenal glands, degeneration and necrosis of the renal tubules, and edema and hyperplasia of the lungs (Treon *et al.*, 1955; U.S. EPA, 1992; U.S. EPA, 1984). U.S. EPA (1992) cited an unpublished 1972 study from International Research and Development Corporation as determining oral LD_{50}s of 630, 530, and 584 mg/kg for male, female, and combined sex groups, respectively, of albino rats.

The Southern Research Institute (SRI) conducted an acute gavage study of hexachloro-cyclopentadiene in Fischer-344 rats and $B6C3F_1$ mice. Hexachlorocyclopentadiene in corn oil was administered to both rats and mice at levels of 0, 75, 150, 300, 600, and 1200 mg/kg. One dose at each of the five levels was administered to five animals of each sex. For both species, clinical observations included decreased activity, ruffled fur, and diarrhea occurring within 6-24 hours of dosing, with severity and duration related to dose level. All rats in the 600 and 1200 mg/kg dose groups, as well as two female rats in the 300 mg/kg dose group died. Ruffled fur and diarrhea occurred in the 75-150 mg/kg dose range. For mice, all animals died in the 1200 mg/kg dose group while only one male and one female died at the 600 mg/kg level. Only minor effects were observed at the lower levels in the mouse. The NOAEL in rats was 150 mg/kg and the NOAEL in mice was 300 mg/kg (Southern Research Institute, 1980a).

In a related subacute study, the SRI conducted a repeated-dose gavage investigation in which F-344 rats and $B6C3F_1$ mice. Hexachlorocyclopentadiene in corn oil was administered to rats at levels of 0, 25, 50, 100, 200, and 400 mg/kg, and to mice at dose levels of 0, 50, 100, 20, 400, and 800 mg/kg. Five rats and mice of each sex were used at each dose level on the following schedule of 12 dosing days: days 1-5, 8-12, 15, and 16 (Southern Research Institute, 1980b). In the rat study, clinical observations revealed all males and 4/5 females died at the 400 mg/kg dose level, while 1/5 males and 4/5 females died at the 200 mg/kg level. Investigators noted significant weight depression but no deaths or life-threatening clinical or gross observations at the 100 mg/kg level; but interestingly there were gross changes to the stomach wall, with no clinical observations, at the 50 mg/kg level. The investigators determined 25 mg/kg as a NOAEL for rats in this experiment (Southern Research Institute, 1980b).

In mice, all animals treated at the 800 mg/kg level died as did two among the 200 mg/kg and one at the 50 mg/kg level. Several of the deaths are attributed to improper dosing and handling techniques. 100 mg/kg was determined by the investigators to be the mouse NOAEL for the subacute repeated-dose study (Southern Research Institute, 1980b).

Acute inhalation toxicology. Rand *et al*. (1982) determined the 4-hour LC_{50} via inhalation exposure to male and female Sprague-Dawley rats. In this study eight groups, each consisting of 10 male and 10 female rats, were exposed to 8 different vapor concentrations of hexachlorocyclopentadiene. The HEX concentrations were 0.28, 1.4, 2.5, 3.1, 3.3, 3.4, 4.0, and 5.8 ppm. The 4-hour LC_{50} and 95 percent confidence limits were 1.6 $\pm$ 0.6 ppm for males and 3.5 $\pm$ 2.1 ppm for females (Rand *et al.*, 1982). In order to compare the acute inhalation toxicity to the acute oral toxicity, we calculated the equivalent inhalation toxicity on a mass basis. After assuming a body weight of 0.267 kg for male rats (the more sensitive sex), and assuming an inhalation rate of 0.27 m^3/day, we calculated the mass dose equivalent to the inhalation LC_{50} of 1.6 ppm for 4 hours was 3.06 mg/kg. In comparison, the acute oral LD_{50} in the rat was determined by Treon *et al.* (1955) to be 505 mg/kg.

Subchronic Toxicity

Subchronic oral toxicology

In a key 13-week study (Abdo *et al.*, 1984) administered hexachlorocyclopentadiene in corn oil by gavage to groups of 10 male and 10 female F334 rats at doses of 0, 10, 19, 38, 75, and 150 mg/kg, and also groups of 10 male and 10 female $B6C3F_1$ mice at doses of 0, 9, 19, 38, 75, 150, and 300 mg/kg. The doses were administered once daily, five days per week for 13 weeks. Deaths due to HEX intoxication occurred at 150 and 300 mg/kg in mice (Abdo *et al.*, 1984).

The authors further reported that hexachlorocyclopentadiene caused stomach lesions of hyperplasia and focal inflammation in male and female mice and male rats at and above 19 mg/kg (Abdo *et al.*, 1984; U.S. EPA, 1992). From the Abdo data, U.S. EPA selected 10 mg/kg HEX for rats as the no-observed-adverse-effects-level for determination of the Drinking Water Equivalent Level (U.S. EPA, 1992). It should be noted that compared with the acute studies mentioned above, HEX is more toxic at lower dose levels when administered in repeated doses, subchronically.

Subchronic inhalation toxicology

Rand *et al.* (1982) performed 90-day inhalation toxicity studies of HEX on the rat and the monkey. The authors exposed Sprague-Dawley rats and cynomolgus monkeys to HEX levels of 0, 0.01, 0.05, and 0.2 ppm. The 320 rats were divided into four groups consisting each of 40 males and 40 females. Forty-eight monkeys were divided into 4 groups consisting of 6 males and 6 females each. Both species were exposed to the above-mentioned HEX levels for 6 hours/day, 5 days/week, for up to 14 weeks. The exposures did not produce measurable clinical or physical responses in either species. The authors did find marginal organ weight changes and hematological changes and attributed these to impaired respiratory function (Rand *et al.*, 1982).

In 1955, Treon and coworkers exposed guinea pigs, rabbits, rats and mice to 0.15 or 0.34 ppm for exposure periods of 7 hours for 5 days/week. The upper dose level was run for 25-30 exposures while the lower level was run for up to 150 exposure periods. At the upper exposure level, guinea pigs survived 30 exposures while only 2/6 rabbits, 0/4 rats, and 0/5 mice survived 5 exposures. Pulmonary edema, acute necrotizing bronchitis, and degenerative changes in the brain, heart, liver, adrenal glands, and kidneys were reported. At the lower concentration 2/2 guinea pigs, 3/3 rabbits, 4/4 rats, and only 1/5 mice survived 150 exposure period (Treon *et al.*, 1955).

Genetic Toxicity

The National Toxicology Program (1994) reviewed the genotoxicity research performed on hexachlorocyclopentadiene. HEX was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without S9 microsomal activation. No induction of sex linked recessive lethal mutations was observed in male *Drosophila melanogaster* treated with HEX by feeding, and no increase in the frequency of micronucleated erythrocytes was seen in male or female $B6C3F_1$ mice exposed to HEX by inhalation for 13 weeks. Hexachlorocyclopentadiene did induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, with and without S9 (NTP, 1994). Results from an older study, which evaluated HEX for sex-linked recessive lethal mutations, were not conclusive (Zimmering *et al.*, 1985). A more recent study re-examined the data and concluded that HEX was not mutagenic via the sex linked recessive lethal mutation protocol (Mason *et al.*, 1992).

Developmental and Reproductive Toxicity

Research to evaluate a broad range of parameters related to reproductive function and success has not been conducted (ATSDR, 1997). Murray *et al. (*1980) evaluated the teratogenic potential of HEX in CF-1 mice and New Zealand rabbits. Both species were given 0, 5, 25, or 75 mg/kg per day via gavage from days 6-15 of gestation (mice) or days 6-18 of gestation (rabbits). A teratogenic effect was not detected in either species and the author interpreted the result as "…little evidence of embryotoxicity" (Murray *et al.*, 1980). RTECS (1997) apparently interpreted the Murray *et al.* (1980) results as yielding specific developmental abnormalities in musculoskeletal system, and this interpretation was apparently used by Kolb (1993) for listing HEX as a chemical which may cause teratogenic effects (Kolb, 1993; RTECS, 1997). Adequate evidence of developmental and reproductive toxicity for animals exposed to HEX is not currently available.

Immunotoxicity

No studies are available which evaluate a broad range of immunological parameters (ATSDR, 1997). Inhalation toxicology studies have not yielded histopathological changes in the spleen, thymus, or lymph nodes of rats or mice exposed subchronically or chronically to hexachlorocyclopentadiene vapors (ATSDR, 1997; Rand *et al.*, 1982; NTP, 1994).

Neurotoxicity

Rabbits and mice exposed via inhalation briefly to high concentrations of HEX (46.5 ppm or greater) occasionally became tremorous (Treon *et al.*, 1955). Additionally, as described earlier, the same authors discovered diffuse degeneration of the brain, along with similar lesions in other tissues of guinea pigs, rabbits, rats, and mice, from subchronic inhalation administration of HEX at doses of 0.34 ppm (Treon *et al.*, 1955). Similarly, Rand *et al.* (1982) exposed rats and monkeys via inhalation to 0.01, 0.05, and 0.2 ppm HEX for six hours/day for five days/week for up to 14 weeks, found no such brain lesions, and inferred that the increased toxicity noted by Treon *et al*. may have resulted from the contaminants present in hexachlorocyclopentadiene tested in 1952 (Rand *et al.*, 1982).

Chronic Toxicity

The National Toxicology Program reported 2-year HEX inhalation studies in the rat and mouse (NTP, 1994). Groups of rats and mice, with 60 male and 60 females per group, were exposed to HEX levels of 0, 0.01, 0.05, or 0.2 ppm for two years. Survival rates of rats were similar to the controls and no chemical related findings, except for respiratory tract intoxication, were observed at any dose level for either sex of rats during the two-year study. One effect was pigmentation of the respiratory epithelium of the nose, trachea (males), and bronchi and bronchioles of the lung. Squamous metaplasia of the laryngeal epithelium occurred in female rats exposed to HEX. In the mouse, suppurative inflammation of the nose as well as pigmentation of the respiratory mucosal epithelium occurred from HEX exposure.

Chronic animal studies examining hexachlorocyclopentadiene exposure via oral and dermal routes were not located. U.S. EPA (1991) reported that a chronic oral study of HEX, which was begun for the NTP, was terminated in April 1982 because *inhalation* was determined to be the more relevant route of exposure.

Carcinogenicity

The NTP (1994) study described above also examined HEX for possible carcinogenic effects. Inhalation exposure of male and female F344/N rats or $B6C3F_1$ mice to levels of 0.01, 0.05, or 0.2 ppm for 2 years yielded no evidence of carcinogenic activity in either sex of either species (NTP, 1994). There is a possibility that since toxic effects appear to be direct effects at the point of entry, or point of exposure, the maximum tolerated dose may be artifactually low, and hence, potential systemic toxicity and potential carcinogenicity may not have been adequately explored in this NTP study. This is especially true for the rat in which no adverse effects were observed on weight gain or survival (NTP, 1994).

Toxicological Effects in Humans

Data are quite limited regarding human health effects of exposure to HEX (U.S. EPA, 1992; ATSDR, 1997).

The following studies and data are listed under the broad exposure category of acute toxicity. It is, however, likely that some of the exposures occurred on a subacute basis, that is, they occurred over a period of more than one day and less than or equal to one month. For the report of Treon (1955) incidental exposures to HEX vapors presumably occurred on more than one day. Hexachlorocyclopentadiene exposure of sewage plant workers in Kentucky occurred during the month of March, 1977, increasing in concentration until the plant was closed on March 28, 1977 (Morse *et al.*, 1979).

Acute Human Toxicity

Treon *et al.*(1955) reported that members of his research team suffered headaches following incidental exposure to low concentrations of hexachlorocyclopentadiene vapors from animal exposure chambers. The concentrations were never estimated.

In 1977, approximately 145-200 workers at the Morris Forman Wastewater Treatment Plant in Louisville, Kentucky were exposed to HEX from contamination by about 6 tons of the material (U.S. EPA, 1992; Morse *et al.*, 1979; Kominsky *et al.*, 1980). Symptoms included eye irritation (59 percent), headache (45 percent), and throat irritation (27 percent) (Morse *et al.*, 1979). Other symptoms included chest discomfort, nausea, and fatigue, with symptoms lasting at least six weeks in 5-18 percent of the exposed workers (Kominsky *et al.*, 1980). Hexachlorocyclopentadiene contamination levels in the water were measured as high as 1000 ppm and air samples of the sewer line were as high as 400 ppm. The highest rates of symptoms were in areas of the plant closest to the sewage influent. Sampling was performed after some of the exposures ended and actual peak worker exposure levels are not known.

The exposures of the plant workers were not solely to hexachlorocyclopentadiene, but rather to a mixture of HEX and octachlorocyclopentene, or OCCD present as sewage contaminants. Kominsky *et al.* (1980) related certain exposures to symptoms. Exposure for several seconds at 19 ppm HEX (and 0.6 ppm OCCD) caused lacrimation, skin irritation, chest discomfort, and nausea. At 7 ppm HEX (and approximately 0.5 ppm OCCD) exposure for several seconds, three persons who were wearing half-face respirators suffered eye and skin irritation (Kominsky *et al.*, 1980).

Health questionnaires supplied by the Centers for Disease Control were completed by 145 plant workers, and the responses are summarized in the following table. Laboratory tests showed no significant abnormalities in renal function tests, complete blood counts, or urinalyses; however, 27 percent of 41 workers tested showed elevated levels of lactic dehydrogenase and 15 percent were found to have proteinuria (Morse *et al.*, 1979; Kominsky *et al.*, 1980).

Table 3. Symptoms of 145 Wastewater Treatment Plant Employees Exposed to Hexachlorocyclopentadiene*

Symptom	Number of Employees Reporting Symptom	Percent of Employees Reporting Symptom
Eye irritation	86	59
Headache	55	45
Throat Irritation	39	27
Nausea	31	21
Skin irritation	29	20
Cough	28	19
Chest Pain	28	19
Difficult breathing	23	16
Nervousness	21	14
Abdominal cramps	17	12
Decreased appetite	13	9
Decreased memory	6	4
Increased saliva production	6	4

*Sources, U.S. EPA table (U.S. EPA 1992), adapted from Morse *et al.* 1978

Subchronic Human Toxicity

Information on the subchronic toxicity of hexachlorocyclopentadiene to humans could not be located.

Human Genetic Toxicity

Information on the genetic toxicity of hexachlorocyclopentadiene to humans could not be located.

Developmental and Reproductive Human Toxicity

Information on the developmental and reproductive toxicity of hexachlorocyclopentadiene to humans could not be located.

Human Neurotoxicity

As mentioned under acute toxicity, Treon *et al.* (1955) reported that members of his research team suffered headaches following incidental exposure to low concentrations of hexachlorocyclopentadiene vapors from animal exposure chambers. The concentrations were never estimated. Similarly, Morse *et al.* (1979) reported that 45 percent of sewage treatment plant workers acutely exposed to HEX in wastewater experienced headaches. Headaches, however, are not necessarily neurotoxic effects.

Chronic Human Toxicity

Other than worker exposure in HEX manufacturing or HEX waste disposal, no other chronic human health effects data from HEX exposure can be found in the literature (U.S. EPA 1992). Epidemiological mortality studies have been performed on workers exposed to HEX. U.S. EPA (1992) reported that epidemiologic studies have generally shown no significant differences in mortality rates between workers exposed to HEX in the workplace and the general population.

Carcinogenicity to Humans

Information on the possible carcinogenicity of hexachlorocyclopentadiene to humans could not be located.

DOSE-RESPONSE ASSESSMENT

Noncancer Toxic Effects

In 1992, U.S. EPA calculated the Drinking Water Equivalent Level (DWEL) for lifetime exposure to hexachlorocyclopentadiene to be 0.25 mg/L, as a function of the oral reference dose (RfD) of 0.007 mg/kg-day (U.S. EPA 1992). The DWEL is a lifetime exposure concentration protective of adverse, noncancer health effects under the assumption that all of the exposure to a contaminant is via drinking water (U.S. EPA, 1996).

The U.S. EPA (1992) cited a 1981 SRI study (Abdo *et al.* 1984) as the only longer-term oral study of significant duration and suitable experimental design that can be used for calculating longer-term health advisories. As described earlier, in this 13-week oral subchronic study, HEX was administered in corn oil by gavage to groups of 10 male and 10 female F334 rats at doses of 0, 10, 19, 38, 75, and 150 mg/kg, and also groups of 10 male and 10 female $B6C3F_1$ mice at doses of 0, 9, 19, 38, 75, 150, and 300 mg/kg. The doses were administered once daily, five days per week for 13 weeks. Deaths due to HEX intoxication occurred at 150 and 300 mg/kg in mice. The authors further reported that HEX caused stomach lesions of hyperplasia and focal inflammation in male and female mice and male rats at and above 19 mg/kg (Abdo *et al.*, 1984; U.S. EPA, 1992). From the Abdo data, U.S. EPA selected 10 mg/kg-day for rats as the NOAEL for determination of the HEX Drinking Water Equivalent Level (U.S. EPA, 1992).

From the NOAEL of 10 mg/kg-day, U.S. EPA determined an RfD for hexachlorocyclopentadiene of 0.007 mg/kg-day by applying a 1000-fold uncertainty factor (10-fold for deriving an NOAEL from an animal study, 10 fold to account for variability among humans, and 10-fold to account for the use of study data “that are significantly less-than-lifetime in duration” to develop a lifetime RfD). We believe that this last 10-fold factor also accounts for any uncertainties arising from methods of dosing. The DWEL is derived from the reference dose by adjusting the RfD to a continuous exposure with a 5/7 correction factor, then assuming an adult male body weight of 70 kg and a daily drinking water consumption of 2 L/day. The DWEL was calculated to be 0.25 mg/L.

OEHHA concurs with U.S. EPA's identification of 10 mg/kg-day as the critical NOAEL. This level is used in the calculation of a PHG for HEX in drinking water.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncancer toxicants must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncancer Effects

The calculation of the public health-protective concentration (C, in mg/L) for hexachlorocyclopentadiene follows a general formula for noncancer endpoints:

$$C = \frac{\text{NOAEL x ECF x RSC x BW}}{\text{UF x L/day}} = \text{PHG in mg/L}$$

where,

NOAEL	=	No-observed-adverse-effect-level (10 mg/kg-day)
RSC	=	Relative source contribution of 40% (0.4). The default is 0.2, however volatile chemicals such as HEX are less likely to be found in food and soil.
BW	=	Body weight for an adult male (70 kg)
ECF	=	Exposure correction factor (five days/seven days, 0.714)
UF	=	Uncertainty factor of 1,000 (10-fold for inter-species variation, 10-fold for human variability, 10-fold to account for the use of a subchronic study for determining a lifetime value and dose by gavage)
L/day	=	Volume of drinking water consumed by an adult (4 L/day). The default is 2L/day, however the higher value accounts for additional inhalation exposure from various uses of drinking water, such as bathing.

Therefore,

$$C = \frac{\underline{10.0 \text{ mg/kg-day} \times 0.714 \times 0.4 \times 70 \text{ kg}}}{1{,}000 \times 4 \text{ L/day}}$$

$$= 0.05 \text{ mg/L} \quad = 50 \text{ ppb.}$$

The PHG for hexachlorocyclopentadiene in drinking water is therefore 0.05 mg/L (50 ppb).

For comparison, U.S. EPA's DWEL calculation (0.25 mg/L) assumes that 100% of the human exposure to HEX derives from drinking water. The RSC is an assumption of the percentage of exposure we would receive via drinking water relative to other potential sources such as food and air. People are not normally exposed to HEX. It does have an identified potential to accumulate in the environment (U.S. EPA, 1984; Lu *et al.*, 1975), however, volatile chemicals such as HEX are less likely to be found in food and soil. A RSC value of 40% exposure from drinking water is most appropriate for HEX.

RISK CHARACTERIZATION

Hexachlorocyclopentadiene is a highly reactive chemical, and generally does not persist or accumulate in the environment. HEX, which is insoluble in water, is also volatile, and detectable amounts are not typically found in drinking water (U.S. EPA 1992; ATSDR 1997). HEX is moderately toxic via the oral route of administration and about 100 times more toxic via the inhalation route (U.S. EPA, 1992). There was no evidence of carcinogenicity found in an NTP rat and mouse study (NTP, 1994; NTP, 1998).

The PHG for hexachlorocyclopentadiene is based on a rigorously conducted subchronic gavage study in rats (Abdo *et al.*, 1984). From this study, a NOAEL of 10 mg/kg-day was identified, and used in the PHG calculation, along with several values to account for uncertainty and differences from daily exposure. The resulting value adequately accounts for potential extra sensitivity of subpopulations, including infants and children. Suitable chronic drinking water studies are not available, nor are suitable human chronic or subchronic studies available that contain well-defined exposure information.

Although the Abdo paper is the best long-term oral study available, it does present some sources of uncertainty which must be mentioned. First, as mentioned previously, this study is only for 90 days. Second, the animals were dosed by gavage rather than via food or water. It is conceivable that different toxic effects might result between a once-daily gavage and a more gradual administration through feed or water. Gavage administration might artifactually overstate toxicity compared with drinking water administration because of the high-concentration, bolus effect. In contrast, calculation of toxicity from oral exposures may significantly understate total toxic effects, because inhaled HEX (due to volatilization from drinking water) is much more toxic than the orally-administered chemical (U.S. EPA, 1992).

OTHER REGULATORY STANDARDS

The current U.S. EPA maximum contaminant level for hexachlorocyclopentadiene is 0.05 mg/L (U.S. EPA, 1996). The California MCL and Recommended Public Health Level (RPHL), are 50 ppb (OEHHA, 1993; Lam *et al.*, 1994). The following table includes selected international, national and state regulations and guidelines for comparison to the recommended PHG.

Table 4. Selected Guidelines And Regulations For Hexachlorocyclopentadiene

Agency	Standard or Criterion	Level	Comment
ATSDR	oral MRL	0.1 mg/kg-day	intermediate duration exposure
NIOSH	REL, TWA	0.01 ppm	recommended occupational inhalation level
U.S. EPA	MCL	0.05 mg/L	water
U.S. EPA	MCLG	0.05 mg/L	safety margin goal
U.S. EPA	DWEL	0.2 mg/L	non-cancer effect protective level
U.S. EPA	Lifetime Health Advisory	0.15 mg/L	lifetime
ACGIH	TLV-TWA	5 mg/m^3	occupational inhalation
California	MCL	0.05 mg/L	previously adopted federal level
California DHS	RHPL	0.05 mg/L	

Table adapted from (ATSDR, 1997; U.S. EPA, 1996; NIOSH, 1994; Lam *et al.*, 1994)

REFERENCES

Abdo KM, Montgomery CA, Kluwe WM, Farnell DR, Prejean JD (1984). Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. *J Appl Toxicol* **4**(2):75-81.

ACGIH (1992). Documentation of the threshold limit values and biological exposure indices. 6th edition. *American Conference of Governmental and Industrial Hygienists* :739-40.

ATSDR (1997). Toxicological Profile for Hexachlorocyclopentadiene. U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry ,1997. Draft for public comment.

Dorough HW, Ranieri TA (1984). Distribution and elimination of hexachlorocyclopentadiene in rats and mice. *Drug Chem Toxicol* **7**(1):73-89.

El Dareer SM, Noker PE, Tillery KF, Hill DL (1983). Investigations on the basis for the differential toxicity of hexachlorocyclopentadiene administered to rats by various routes. *J Toxicol Environ Health* **12**(2-3):203-11.

Grosjean and Williams (1992). Environmental persistence of organic compounds estimated from structure-reactivity and linear free-energy relationships, unsaturated aliphatics. *Atmos Environ* **8**:1395-405.
As cited in ATSDR 1997.

Kolb DK (1993). Teratogenic chemicals in undergraduate chemistry laboratories. *Kolb, V. M. (Ed.). Teratogens: Chemicals Which Cause Birth Defects, 2nd Edition. Elsevier: Amsterdam, Pp. 75-92.*

Kominsky JR, Wisseman CL 3d, Morse DL (1980). Hexachlorocyclopentadiene contamination of a municipal wastewater treatment plant. *Am Ind Hyg Assoc J* **41**(8):552-6.

Lam R HF, Brown JP, Fan AM (1994). Chemicals in California drinking water: source of contamination, risk assessment, and drinking water standards. *In: Wang, R. G. M. (Ed.). Environmental Science And Pollution Control Series, 9. Water Contamination And Health: Integration Of Exposure Assessment, Toxicology, And Risk Assessment. Marcel Dekker, Inc.: New York* .

Lawrence LJ, Dorough HW (1982). Fate of inhaled hexachlorocyclopentadiene in albino rats and comparison to the oral and IV routes of administration. *Fundam Appl Toxicol* **2**(5):235-40.

Lawrence LJ, Dorough HW (1981). Retention and fate of inhaled hexachlorocyclopentadiene in the rat. *Bull Environ Contam Toxicol* **26**(5):663-8.

Lu PY, Metcalf RL, Hirwe AS, Williams JW (1975). Evaluation of environmental distribution and fate of hexachlorocyclopentadiene, chlordane, heptachlor, and heptachlor expoxide in a laboratory model ecosystem. *J Agric Food Chem* **23**(5):967-73.

Mason JM, Valencia R, Zimmering S (1992). Chemical Mutagenesis Testing in Drosophila: VIII. Reexamination of Equivocal Results. *Environ Molec Mutagen,* **19**(3): 227-34 .

Morse DL, Kominsky JR, Wisseman CL 3d, Landrigan PJ (1979). Occupational exposure to hexachlorocyclopentadiene. How safe is sewage? *JAMA* **241**(20):2177-9.

Murray FJ, Schwetz BA, Balmer MF, Staples RE (1980). Teratogenic potential of hexachlorocyclopentadiene in mice and rabbits. *Toxicol Appl Pharmacol* **53**(3):497-500.

NIOSH (1994). Pocket guide to chemical hazards. *U.S. Department of Health and Human Services. DHHS (NIOSH) Publication # 94-116* .

NTP (1998). Management Status Report. *National Toxicology Program, Division of Toxicology Research and Testing* .
NIEHS, Box 12233, RTP, NC 27709.

NTP (1994). Toxicology and carcinogenesis studies of hexachlorocyclopentadiene in F344/N rats and B6C3F1 mice (inhalation studies). *National Toxicology Program Technical Report Series; 437;* 318p.

OEHHA (1993). Memorandum. *Review of U.S. EPA's Final Rule of Phase V Chemicals* . Adopts U.S. EPA MCL of 0.05 mg/L as state RPHL value for hexachlorocyclopentadiene.

Podowski AA, Sclove SL, Pilipowicz A, Khan MA (1991). Biotransformation and disposition of hexachlorocyclopentadiene in fish. *Arch Environ Contam Toxicol* **20**(4):488-96.

Rand GM, Nees PO, Calo CJ, Alexander DJ, Clark GC (1982). Effects of inhalation exposure to hexachlorocyclopentadiene on rats and monkeys. *J Toxicol Environ Health* **9**(5-6):743-60.

RTECS (1997). Registry of Toxic Effects of Chemical Substances. *U.S. Dept. of Health and Human Services. NIOSH* .Micromedex Inc. Vol. 32.

Southern Research Institute (1980a). Acute toxicity report on hexachlorocyclopentadiene in Fischer-344 rats and B6C3F1 mice. *Unpublished Report for NTP* . As cited in U. S. EPA 1991.

Southern Research Institute (1980b). Repeated-dose toxicity report on hexachlorocyclopentadiene (C53607) in Fischer-344 rats and B6C3F1 mice. *Unpublished Report for NTP*. As cited in U. S. EPA 1991.

Treon J, Cleveland F, and Cappel J (1955). The toxicity of hexachlorocyclopentadiene. *Arch Ind Health 11:459*-72.

U.S. EPA (1980). Ambient Water Quality Criteria for Hexachlorocyclopentadiene. U. S. Environmental Protection Agency, Office of Water Regulations and Standards, EPA 440/5-80-055, 1980.

U.S. EPA (1984). Health Assessment Document for Hexachlorocyclopentadiene. Office of Health and Environmental Assessment. *EPA-600/8-84-001F*. U.S. EPA (1995). Drinking water and health, consumer and technical fact sheets on: hexachlorocyclopentadiene. *EPA 811-F-95-003-T* . Office of Water.

U.S. EPA (1992). Drinking water criteria document for hexachlorocyclopentadiene. Environmental Criteria and Assessment Office, Cincinnati, OH: 1992.
PB92-173418.

U.S. EPA (1996). Drinking Water Regulations and Health Advisories. Office of Water,1996. EPA 822-B-96-002.

WHO (1991a). Health and Safety Guide for Hexachlorocyclopentadiene . World Health Organization. *Health and Safety Guide Number 63*. Geneva: 1991a.

WHO (1991b). Hexachlorocyclopentadiene: Environmental Health Criteria 120. World Health Organization,1991b.

Wolfe N, Zepp R, Schlotzhaver P, Sink M (1982). Transformation pathways of hexachlorocyclopentadiene in the aquatic environment. *Chemosphere* **11**(2):91-101.
As cited in W.H.O. 1991b.

Yu C, Atallah Y (1981). Pharmacokinetics and metabolism of hexachlorocyclopentadiene in rats. *Report No. 10. Project No. 482428. Velsicol Chemical Corporation, Chicago, Ill.*
As cited in ATSDR (1997) and U.S. EPA (1984).

Zimmering S, Mason JM, Valencia R, Woodruff RC (1985). Chemical mutagenesis testing in Drosophila. II. Results of 20 coded compounds tested for the National Toxicology Program. *Environ Mutagen* **7**(1):87-100.